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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,353	04/27/2001	Gary Ruvkun	00786/351005	3561

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 07/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/844,353	RUVKUN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,13,17 and 19-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,13, 17 and 19-2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/24/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 04/21/05 has been acknowledged.

Claims 1, 13, 17, 19-24 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Note: A non-final office action has been issue herein to address written description and enablement issues newly raised in this office action.

Claim Rejections - 35 USC § 112

Claims 1, 13, 17 and 19-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a method for screening candidate modulatory compounds for ameliorating or delaying an impaired glucose tolerance condition, atherosclerosis or obesity comprising: providing a C. elegans or isolated C. elegans cell expressing a gene that encodes any variant of SEO ID NO:54, SEQ ID NO:57, SEQ ID

NO:102, human FKHR gene or human AFX gene that functions in insulin signaling; and contacting the C. elegans or isolated C. elegans cell with a candidate compound, wherein a decrease in expression or activity of the gene with the candidate compound identifies a candidate modulatory compound for ameliorating or delaying an impaired glucose tolerance condition, atherosclerosis or obesity.

At best the specification discloses the amino acid sequences of SEQ ID NO:54 which represent an amino acid motif at location 242-344 of *C. elegans* daf-16 protein (spec. page 77, para.2). Based upon the degree of amino acid homology (Spec. fig-21A), the specification teaches that FKHR and AFX are human orthologs of C. *elegans's* daf-16 (Spec. fig-21B).

Besides the amino acid sequences of SEQ ID NO:54 (def-16 motif) the specification as filed fails to disclose what encompass a gene comprising any variant of SEQ ID NO:54 that functions in insulin signaling. Similarly the specification as filed fails to disclose any gene comprising any variant of SEQ ID NO:57 and 102 that hybridizes under stringent conditions to the nucleic acid encoding the amino acid sequences of SEQ ID NO:57 and 102 respectively. Furthermore the specification fails to disclose what represent human FKHR and AFX gene especially in view of the fact that the scope of gene encompasses not only the ORF but also regulatory regions and the genomic sequence etc .

Furthermore besides human FKHR and AFX encoding sequences the specification fails to disclose any other gene that comprises any variant of SEQ ID NO:57 and SEQ:102, wherein the gene is obtained form any other organism and is capable of functioning like an insulin signals and convergence with DAF-7-like Smad signals. The specification as filed fails to identify the relevant characteristics of the gene (as claimed) such that a person skilled in the art would recognize the human FKHR and human AFX genes. For example the specification fails to disclose the nucleotide sequence, which comprises a gene encoding human FKHR and AFX genes comprising not only ORFs, but also regulatory regions and the genomic sequence etc.

Response to arguments

The applicant argues that the specification provides a written description of the presently claimed invention in sufficient detail to satisfy the standard set forth by the Patent Office is its Written Description Guidelines and by the Federal Circuit in Lilly. The applicant argues that the specification, for example, in Figure 21A discloses the human FKHR and AFX sequences and shows an alignment between DAF-16 (including SEQ ID NO:54) and these human sequences. The applicant argues that the in view of this Figure (21A), one skilled in the art would recognize that the human FKHR and AFX sequences are highly similar to the sequence of SEQ ID NO:54. The applicant argues that inventor Dr. Galy Ruvkun has demonstrated that at least one of these variants can functionally substitute for daf-16 in-vivo. The applicant argues that the in view of these experiments, there can be no question that Applicants' specification satisfies the written description requirement. Regarding the hybridization variants the applicant argues that these claims also clearly satisfy the written description requirement especially in view of written description guidelines. The applicant argues that the claim 17 encompasses a nucleic acid molecule that specifically hybridizes to the complement of the sequence set forth in SEQ ID NO:54 under highly stringent conditions. Regarding FKHR and AFX genes the applicant argues that the amino acid sequences of these polypeptides need not to be disclosed in the specification, as the sequences of these human genes were known in the art at the time of filing.

However, applicant's argument are found not persuasive because scope of invention as claimed is not limited to nucleic acid encoding polypeptide of SEQ ID NO:54, SEQ ID NO:57, SEQ ID NO:102, human FKHR or human AFX but a gene that encodes a polypeptide having 95% identity to SEQ ID NO:54, a gene that hybridizes to nucleic acid of SEQ ID NO:57 or SEQ ID NO:102, a human FKHR gene and human AFX gene. Since the scope of a gene encompasses not only the ORF but also regulatory regions and the genomic sequence etc, the invnetion as claimed fails to meet the written description requirements especillay in view of *Written Description Requirement* and by the Federal Circuit in Lilly. As stated earlier the disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when

the specification fails to describe the features of that genus, even in passing. (see In re Shokal 113USPQ283(CCPA1957); Purdue Pharma L. P. vs Faulding Inc. 56 USPQ2nd 1481 (CAFC 2000). In the instant case the specification only discloses the amino acid sequences of daf-16 (SEQ ID NO:54) and daf-16 human orthologs FKHR and AFX. The specification fails to disclose any gene that is a variant of SEQ ID NO:54, FKHR and AFX and has the functional property of an insulin signaling polypeptide explicitly or implicitly as putatively claimed herein.

The possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with *sufficient relevant identifying characteristics* (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *See, e.g., Pfaff v. WellsElectronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991).* In the instant case the genes as claimed has been defined only by a statement of function that broadly encompasses an insulin signaling like activity, which conveyed no distinguishing information about the identity of the claimed genetic sequence, such as its relevant structural or physical characteristics like regulatory regions and the genomic sequence etc.

The scope of claim 1 also encompasses any gene containing variation in the conserved motif (SEQ ID NO:54), which is considered germane to the functional activity of daf-16 polypeptide. For example 5% variation (95% identical) in the conserved domain of a gene or a hybridization product as claimed would certainly affect proper folding and biological activity if amino acids that are critical for such functions are substituted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. Furthermore, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo and Rudinger). According to these facts, one skill in the art would

conclude that applicant was not in the possession of the claimed genus because a description of only one member (daf-16 motif) of this genus is not representative of the variants of genus (all related genes) and is insufficient to support the claim.

Claims 1, 13, 17 and 19-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of Invention:

The instant invention relates to a method for identifying a compound that ameliorate or delay an impaired glucose tolerance condition atherosclerosis or obesity.

Breadth of Claims and Guidance Provided in the Specification

The instant claims are drawn to a method for screening candidate modulatory compounds for ameliorating or delaying an impaired glucose tolerance condition, atherosclerosis or obesity comprising: providing a C. elegans or isolated C. elegans cell expressing a gene that encodes any variant of SEO ID NO:54, SEQ ID NO:57, SEQ ID NO:102, human FKHR gene or human AFX gene that functions in insulin signaling; and contacting the C. elegans or isolated C. elegans cell with a candidate compound, wherein a decrease in expression or activity of the gene with the candidate compound identifies a candidate modulatory compound for ameliorating or delaying an impaired glucose tolerance condition, atherosclerosis or obesity.

At best the specification discloses the amino acid sequences of SEQ ID NO:54 which represent an amino acid motif at location 242-344 of *C. elegans* daf-16 protein (spec. page 77, para.2). Based upon the degree of amino acid homology (Spec. fig-21A), the specification teaches that FKHR and AFX are human orthologs of C. *elegans's* daf-16 (Spec. fig-21B). Besides the amino acid sequences of SEQ ID NO:54 (def-16 motiff) the specification as filed fails to disclose what encompass a gene comprising any variant of SEQ ID NO:54 that functions in insulin signaling. Similarly the

specification as filed fails to disclose any gene comprising any variant of SEQ ID NO:57 and 102 that hybridizes under stringent conditions to the nucleic acid encoding the amino acid sequences of SEQ ID NO:57 and 102 respectively. Furthermore the specification fails to disclose what represent human FKHR and AFX gene especially in view of the fact that the scope of gene encompasses not only the ORF but also regulatory regions and the genomic sequence etc. Furthermore besides human FKHR and AFX encoding sequences the specification fails to disclose any other gene that comprises any variant of SEQ ID NO:57 and SEQ:102, wherein the gene is obtained form any other organism and is capable of functioning like an insulin signals and convergence with DAF-7-like Smad signals. The specification as filed fails to identify the relevant characteristics of the gene (as claimed) such that a person skilled in the art would recognize the human FKHR and human AFX genes. For example the specification fails to disclose the nucleotide sequence, which comprises a gene encoding human FKHR and AFX genes.

Response to arguments

Regarding the role of daf-16, AFX and FKHR in impaired glucose tolerance condition the applicants argument has been found persuasive especially in view of Dr. Ruvkun's declaration, which establishes that human FKHR can functionally substitute for DAF-16 in C. elegans. Regarding the role of daf-16, AFX and FKHR in arteriosclerosis and obesity the applicant arguments that atherosclerosis and obesity are well established in the art as being impaired glucose tolerance conditions has been found persuasive, especially in view cited references.

However, the claims stand rejected because the scope of claims encompasses any gene that encodes any variant of SEO ID NO:54, SEQ ID NO:57, SEQ ID NO:102, human FKHR gene or human AFX gene that functions in insulin signaling. Since the specification fails to disclose what represent a gene that encodes a polypeptide having 95% identity to SEQ ID NO:54, a gene that hybridizes to nucleotides of SEQ ID NO:57 or SEQ ID NO:102, and human FKHR and AFX gene, it is unclear how one skilled in the art would use the invention as claimed without further undue amount of experimentation, especially in view of the fact that identification of a gene encompasses

not only the ORF but also regulatory regions and the genomic sequence etc. Furhtermore the genes as claimed encompasses variation in the conserved motif (SEQ ID NO:54) or a hybridization product that binds SEQ ID NO:57 or SEQ ID NO:102, which is considered germane to the functional activity of daf-16 polypeptide. For example 5% variation (95% identical) or more (hybridization product) in the conserved domain of a gene or a hybridization product as claimed would certainly affect proper folding and biological activity if amino acids that are critical for such functions are substituted, since the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. Furthermore, mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues (see Ngo and Rudinger). According to these facts, one skill in the art would conclude that it would require an undue amount of experimentation to practice the instant invention, since the description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

In instant case identification of candidate compounds that ameliorate or delay an impaired glucose tolerance condition, atherosclerosis or obesity by evaluating the expression of a polypeptide encoded by an uncharacterized daf-16, AFX or FKHR like gene is not considered routine in the art and without sufficient guidance to the gene sequence i.e. ORF, regulatory regions and the genomic regions etc. the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**.

Sumesh Kaushal
Examiner GAU 1633

SUMESH KAUSHAL
PATENT EXAMINER